REMARKS

Claims 1-14, 24-30, 46-52 and 55-65 appear in this application for the Examiner's review and consideration. Claims 2, 46 and 55 have been amended to require a replication-deficient lentogenic oncolytic strain of NDV; claims 4, 14, 28 and 65 have been amended to specify a HUJ strain comprising the nucleotide sequence as set forth in SEQ ID NO: 1; claims 51 and 52 have been amended to change their dependency; and claim 50 has further been amended to specify an isolated polynucleotide of NDV which encodes at least one polypeptide of NDV. Claims 15-23, 31-45 and 53-54 have been cancelled in a previous amendment. The claim amendments are supported by the specification, specifically by Example 7 on p. 26 lines 4-19, p. 18 line 1 – p. 20 line 34, and p. 5 lines 15-18. Specifically, as further explained below, Example 7 demonstrates that HUJ, which is a lentogenic strain of NDV, is replication-deficient, i.e., cannot replicate efficiently in chicken embryo fibroblast cultures. As no new matter is introduced, their entry at this time is warranted.

Claims 6-14 and 55-65 have been withdrawn from consideration by the Examiner as being drawn to a nonelected invention. It is respectfully submitted that the restriction be withdrawn as to claims 6-14 and 55-65, and that the claims be rejoined. The Examiner incorrectly notes that the election dated September 14, 2005 was made without traverse. The applicants refer the Examiner to p. 8 of the response dated September 14, 2005 where the election was in fact traversed. Further, claim 55, drawn to a method for treating cancer using a polynucleotide encoding NDV, forms part of the elected invention of Group I, as acknowledged by the Examiner in the previous office action dated August 18, 2005. In addition, claims 6-14 depend from claim 2 - an elected claim, and thus should be rejoined upon allowance of claim 2. Similarly, claim 56 should be rejoined when claim 55 is allowed and claims 57-65 should be rejoined when claim 46 is allowed. Therefore, the restriction should be withdrawn and all of the claims should be examined together.

In the office action, the Examiner acknowledges that claim 1 is allowable.

Claims 46 and 50 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, for the reasons set forth on pages 3-5 of the office action. The Examiner states that the specification provides support for polynucleotides encoding NDV polypeptides having oncolytic activity. In response, claims 46 and 50 were

amended to require at least one isolated polynucleotide encoding at least one polypeptide of NDV. Accordingly, the rejection has been overcome and should be withdrawn.

Claims 4, 5 and 28-30 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement, for the reasons set forth on pages 5-7 of the office action. The Examiner states that since the HUJ strain is not known and readily available or can be reproducibly made without undue experimentation, a deposit should be made under the terms of the Budapest Treaty, as required by 37 CFR 1.801-1.809. In response, in accordance with 37 CFR 1.809(b)(1), the applicants assure the United States Patent And Trademark Office that an acceptable deposit will be made during pendency of the instant application. Accordingly, the rejection should be held in abeyance at this time.

Claims 4, 5, 28, 51 and 52 were rejected under 35 U.S.C. §112, second paragraph as being indefinite, for the reasons set forth on page 7 of the office action. In response, claims 4, 5 and 28 have been amended to require that the HUJ strain comprises the nucleotide sequence of SEQ ID NO: 1. Support for this amendment is found on p. 18 line 1 – p. 20 line 34 of the present specification. Furthermore, claims 51 and 52 were amended to change their dependency. Therefore, these rejections have been overcome and should be withdrawn.

Claims 2-5 were rejected under 35 U.S.C. §102(e), as being anticipated by Roberts et al. (US 2003/0044384), for the reasons set forth on page 8 of the office action. The Examiner asserts that Roberts teaches a lentogenic oncolytic strain of NDV.

Claims 2-5, 24-28 and 46-52 are rejected under 35 U.S.C. §102(e), as being anticipated by Groene et al. (US 2003/0077819), for the reasons set forth on page 9 of the office action. The Examiner asserts that Groene teaches a method of treating a human with cancer by administering a composition comprising lentogenic NDV and a physiologically acceptable solution.

The rejections in view of Roberts and Groene are both respectfully traversed, and will be addressed together. Roberts teaches oncolytic interferon-sensitive clonal RNA or DNA viruses, and explicitly requires that the oncolytic virus is replication-competent, which is defined in the specification as a virus that "produces infectious progeny in neoplastic cells" (see, e.g., p. 3 para. [0033], p. 6, para. [0097] and the claims on p. 25-28. Emphasis added). Moreover, Roberts teaches that "efficient replication of NDV is crucial for the ability of the virus to kill infected cells" (see, p. 5 para. [0078]. Emphasis added). Similar to Roberts, Groene teaches a method of treating a human subject by administering a pharmaceutical composition comprising human

leukocytes and a replication-competent oncolytic virus. As in Roberts, the term "replication-competent" virus is defined by Groene as "a virus that produces infectious progeny in cancer cells" (see, e.g., p. 1 para. [0011], p. 2 para. [0022] and the claims on p. 7-9. Emphasis added).

In contrast, the present invention discloses a replication-deficient lentogenic oncolytic strain of NDV, which produces mostly non-infectious progeny in a host cell. As explicitly disclosed in Example 7 of the specification, HUJ, which is a lentogenic strain of NDV, cannot replicate efficiently in chicken embryo fibroblast cultures. HUJ can replicate efficiently and induce cytopathic effect only under non-natural conditions, i.e., upon addition of trypsin (the $TCID_{50}$ values in the absence of trypsin are $\sim 10^{2.5}$ while in the presence of trypsin the $TCID_{50}$ values are $\sim 10^{8.5}$, see Table 5 on p. 26). Thus, according to the present invention, the replication of a lentogenic NDV is not efficient and the virus is thus replication-deficient, in direct contrast to the replication-competent viruses of Roberts and Groene, which produce infectious progeny in a host cell.

Furthermore, Roberts provides examples of mesogenic oncolytic strains of NDV only, e.g., clones derived from the mesogenic strains MK107, Roakin-1946, and Connecticut 70726-1946, all of which are replication-competent and produce infectious progeny in the infected cells (see Examples 1, 21 and 22, respectively). The present invention, however, teaches away from mesogenic oncolytic strains of NDV. The present invention relates only to replication-deficient lentogenic oncolytic strains of NDV which produce mostly non-infectious progeny.

As recognized by the Examiner, Roberts and Groene do disclose lentogenic strains at one instance (p. 1 para. [0105] in Roberts and p. 2 para. [0028] in Groene), however, Roberts' and Groene's statements that lentogenic strains are useful goes against the rest of their teachings and certainly does not operate in the same way as the replication competent mesogenic strains. Thus, Roberts' and Groene's statements with respect to lentogenic strains are not enabled and are insufficient to motivate a skilled artisan to utilize replication-deficient lentogenic strains in such compositions or treatment method.

Applicants further emphasize that the present invention teaches the unexpected finding that the cytopathic effect exerted by a lentogenic oncolytic strain of NDV does not require efficient viral replication and is not dependent on the production of infectious progeny. For example, the present invention teaches that adsorption of viral surface glycoproteins to tumor cells is sufficient to exert cytotoxic effect on tumor cells. The cytotoxic effect of the surface

glycoproteins on tumor cells is achieved independently of whether the surface glycoproteins are derived from lentogenic or mesogenic strains of NDV (see p. 30 lines 17 through p. 31 line 15 including Fig. 6 and Table 8 of the instant specification). These viral surface glycoproteins do not have the capability to replicate nor to produce infectious progeny. Thus, the findings that isolated glycoproteins exert cytopathic effect in tumor cells further confirm the conclusion that the cytopathic effect exerted by HUJ does not require efficient viral replication. This directly contrasts the disclosure of Roberts and Groene, which explicitly require viral replication in order to induce the cytopathic effect.

Thus, the applicants contend that Roberts and Groene do not anticipate independent claims 2 and 46. As claim 2 and 46 are not anticipated, claims 3-5, 24-28 and 47-52, which are dependent thereon, are also not anticipated. With specific reference to claims 4 and 28, the Examiner states that "the term "HUJ strain" in these claims reads on a clonal lentogenic NDV derived from a natural lentogenic NDV because ...there is nothing in the instant specification to indicate that the HUJ strain is structurally distinct from a NDV derived from lentogenic NDV". Applicants respectfully disagree. The DNA sequence of HUJ is different from known lentogenic NDV. For example, the DNA sequence covering the F gene and most of the HN gene of HUJ is different from the corresponding known DNA sequence of LaSota strain (de Leeuw, O. et al. J. Gen. Virol. 80: 131-136, 1999) in three nucleotides at positions 111, 1006 and 1648 in the F gene (see p. 20 lines 42-44 of the specification). This results in the generation of F protein of HUJ having one amino acid residue different from that of LaSota. Also, the DNA sequence covering the F gene and most of the HN gene of HUJ is different from the corresponding known DNA sequence of B1 strain (Nakaya, T. et al. J Virol. 75: 11868-11873, 2001) in 31 nucleotides. This results in the generation of F and HN proteins of HUJ having six amino acid residues different from those of B1 strain (Nakaya, T. et al. J Virol. 75: 11868-11873, 2001). Thus, the HUJ is structurally distinct from known lentogenic NDV. For this additional reason, claims 4 and 28 are not anticipated.

Moreover, the Examiner has acknowledged the allowability of claim 1, which is drawn to an oncolytic strain of NDV, comprising the nucleotide sequence of SED ID NO: 1. Thus, claims 4 and 28, drawn to a pharmaceutical composition comprising said strain, and method of use thereof for treating cancer, are also allowable for the same reasons claim 1 is allowable.

Based on the foregoing, applicants respectfully submit that each of Roberts and Groene do not anticipate claims 2-5, 24-28 and 46-52, and accordingly the rejections in view of these references should be withdrawn.

Claims 2-5, 24-30 and 46-52 were rejected under 35 U.S.C. §103(a), as being unpatentable over Roberts, for the reasons set forth on pages 10-11 of the office action, The Examiner asserts that it would have been obvious to use lentogenic NDV in a method of treating cancer in a patient, and that one or ordinary skill in the art would have been motivated to use lentogenic NDV in the method in view of Roberts. The applicants respectfully disagree. As explained in detail above, Roberts teaches oncolytic interferon-sensitive clonal RNA or DNA viruses, that are replication-competent, i.e., produce infectious progeny in neoplastic cells. Roberts further teaches that efficient replication of NDV is crucial for the ability of the virus to kill infected cells. In contrast, the present invention discloses a replication-deficient lentogenic oncolytic strain of NDV, which inefficiently replicates and produces mostly non-infectious progeny in a host cell. Furthermore, Roberts provides examples of mesogenic oncolytic strains of NDV only, in contrast to the present invention, which teaches away from mesogenic oncolytic strains of NDV, and relates only to replication-deficient lentogenic oncolytic strains of NDV. Although Roberts discloses lentogenic strains at one instance, Roberts' statements that lentogenic strains are useful goes against the rest of his teachings and certainly does not operate in the same way as the replication-competent mesogenic strains. Thus, Roberts' statements with respect to lentogenic strains are not enabled and are insufficient to motivate a skilled artisan to utilize replication-deficient lentogenic strains in such compositions or treatment method. Therefore, for the same reasons delineated above, the applicants respectfully submit that the present invention is not anticipated, nor is it obvious in view of Roberts, and accordingly the rejection should be withdrawn.

As applicants have distinguished all claims from the closest art of record, it is believed that the entire application is now in condition for allowance. Accordingly, withdrawal of the rejections and allowance of all present claims is respectfully solicited.

Respectfully submitted,

1/18/2006
Date

Yael Webb (Reg. No. 56,633)
For: Allan A. Fanucci (Reg. No. 30,256)

WINSTON & STRAWN LLP
Customer No. 28765

212-294-3311

NY:1005033.1